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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/047,652	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-55,57-64,66-68,70,72-75 and 77-82* is/are pending in the application.

4a) Of the above claim(s) *58-63 and 66-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-55,57,64,70,72-75 and 77-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 56, 65, 71, 76, and adds new claims 81-82, which are related to claims 53-55, 57, 64, 70, 72-75, 77-80, and are not new matter.

Accordingly, claims 53-55, 57, 64, 70, 72-75, 77-82 are being examined.

The following are the remaining rejections.

OBJECTION

Claims 53-55, 57, 64, 70, 72-73 are objected to, because it seems that by typographic error the word "of " after complement is missing in claim 53.

For the purpose of compact prosecution, it is assumed that claim 53 is drawn to an isolated nucleic acid that contains a nucleotide sequence that is the complement "of" SEQ ID NO:1 or SEQ ID NO:2, and hybridizes to at least a portion of a gene for a peripheral-type benzodiazepine receptor (PBR) that encodes SEQ ID NO:3, wherein said nucleic acid inhibits the expression of the gene in a cell line that expresses said PBR gene.

REJECTION UNDER 35 USC 112 FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 53-55, 57, 64, 70, 72-75, 77-80 pertaining to lack of a clear written description remains for reasons already of record in paper of 12/27/04.

New claims 81-82 are rejected for the same reasons of record.

Applicant argues that the claims as amended are directed to a sequence that is complementary to SEQ ID NO:1 or 2, and capable of hybridizing to nucleic acid encoding SEQ ID NO:3, and inhibiting expression of PBR nucleic acid. Applicant argues that in view of the disclosure in the specification, Applicant was in possession of the claimed invention.

Applicant's arguments set forth in paper of 06/29/05 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that a complement of SEQ ID NO:1 or 2 could be a partial or full length complete complement of SEQ ID NO:1 or 2, wherein a partial complement could share with SEQ ID NO:1 or 2 a few complementary nucleotides.

It is further noted that since the specific conditions of hybridization are not recited in the claims, the hybridization conditions could range from very low to very high stringency, and that under very low stringency any unrelated sequences could hybridize or attach to SEQ ID NO:1 or 2.

Moreover, even under the highest stringent hybridization conditions, the claimed complement encompasses unrelated sequences that share with SEQ ID NO:1 or 2 a complementary fragment, via which fragment the claimed complement would hybridize to SEQ ID NO:1 or 2.

Further, it is noted that the language "is" from claim 74, as drawn to a pharmaceutical composition comprising an isolated nucleic acid that "is" a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, wherein the isolated nucleic acid hybridizes to

nucleic acid encoding SEQ ID NO:3 could be reasonably interpreted as having the same meaning as the open language "comprises".

In addition "nucleic acid encoding SEQ ID NO:3" in claim 74 is interpreted as a nucleic acid "comprising" the polynucleotide sequence encoding SEQ ID NO:3, which is only a fragment.

In other words, claim 74 encompasses a pharmaceutical composition comprising an unrelated sequence that share a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, said sequence hybridizes to unrelated sequences attached to the polynucleotide sequence encoding the polypeptide fragment of SEQ ID NO:3.

Similarly, "a PBR gene" as written in claim 74 encompasses any variant PBR gene with unknown structure.

Further, a PBR protein that "comprises" the mutant residues threonine 147 or arginine 162, as claimed in claim 75, or that "comprises" SEQ ID NO:3, as claimed in claims 77, 80, 82, encompasses variant PBR with unknown structure that contains the mutant residues threonine 147 or arginine 162, or unknown sequences that are attached to the polypeptide fragment of SEQ ID NO:3.

Thus the claims encompass a genus of nucleic acids with unknown structure.

The specification and the claims clearly fail to describe the claimed nucleic acids in a manner that satisfy the standards set out in the examples of Lilly and Enzo.

There is no disclosure of the structure of the specific small antisense, complementary fragments of the mutated PBR polynucleotide fragment, SEQ ID NO:1 or 2, that could inhibit expression of the gene PBR encoding SEQ ID NO:3, nor the

polypeptide fragment consisting of SEQ ID NO:3, nor any variant PBR gene, other than the polynucleotide fragment consisting of SEQ ID NO:1 or 2.

The specification clearly lacks disclosure of: 1) a representative species of the claimed genus of nucleic acids, 2) structural features common to the members of the genus of nucleic acids, or 3) a correlation between structure and the function of inhibition of cell proliferation.

The disclosure of the mutated PBR polynucleotide fragment consisting of SEQ ID NO:1 or 2, encoding the polypeptide fragment consisting of SEQ ID NO:3, does not provide a description of the claimed genus of complements that inhibit cell proliferation, or nucleic acids "comprising" a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, or full length PBR gene encoding SEQ ID NO:3, or PBR gene encoding a PBR protein that "comprises" the mutant residues threonine 147 or arginine 162, or that "comprises" SEQ ID NO:3, or any variant PBR genes.

In conclusion, the specification and the claims do not meet the 112, first paragraph, written description requirements, and one would reasonably conclude that Applicant did not have possession of the claimed nucleic acids at the time the invention was made.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

A. Claims 53-55, 57, 64, 70, 72-75, 77-80 and new claims 81-82 are rejected under 112, first paragraph, because the specification, while being enabled for a polynucleotide sequence consisting of SEQ ID NO:1 or 2, or a nucleic acid consisting of

a polynucleotide sequence encoding a polypeptide consisting of SEQ ID NO:3, lacks enablement for complements of SEQ ID NO:1 or 2, that inhibit cell proliferation, or of nucleic acids "comprising" a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, or full length PBR gene encoding SEQ ID NO:3, or PBR gene encoding a PBR protein that "comprises" the mutant residues threonine 147 or arginine 162, or that "comprises" SEQ ID NO:3, or "a PBR gene".

I) Applicant argues that the claims are amended to direct to a sequence that is complementary to SEQ ID NO:1 or 2, and capable of hybridizing to nucleic acid encoding SEQ ID NO:3, and inhibiting expression of PBR nucleic acid.

Applicant argues that in view of the Examiner's acknowledgment that SEQ ID NO:1 or 2 could potentially inhibit PBR expression, the amended claims render the enablement rejection of claims 53-57 and 64 moot.

Applicant's arguments set forth in paper of 06/29/05 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that SEQ ID NO:1 or 2 encoding SEQ ID NO:3 are only cDNA fragments.

One cannot predict whether the claimed complement, which could be of any length, including a few nucleotides, could inhibit cell proliferation for the following reasons:

Although the full length mutated SEQ ID NO:1 and 2, which are relatively large pieces of cDNA (650 bp), potentially could inhibit PBR expression, and although the wild type PBR gene sequence is known, however, since the structure of the mutated, full

length mutated PBR gene comprising the mutated fragment consisting of SEQ ID NO:1 or 2 is not known, and since one cannot predict that the active small antisense sequence(s), such as that of 7 to 40 nucleotides, is within the cDNA fragment consisting of SEQ ID NO:1 or 2, in view that the position of the active antisense sequence on a gene could not be predicted, as taught by US 5,585,479, of record, it would be undue experimentation for one of skill in the art to make the encompassed complementary oligonucleotide sequences that could inhibit expression of the mutated PBR gene.

Further, a complement of SEQ ID NO:1 or 2 could be a partial or full length complete complement of SEQ ID NO:1 or 2, wherein a partial complement could share with SEQ ID NO:1 or 2 a few complementary nucleotides.

In addition, since the specific conditions of hybridization are not recited in the claims, the hybridization conditions could range from very low to very high stringency, and that under very low stringency any unrelated sequences could hybridize or attach to SEQ ID NO:1 or 2.

Moreover, even under the highest stringent hybridization conditions, the claimed complement encompasses unrelated sequences that share with SEQ ID NO:1 or 2 a complementary fragment, via which fragment the claimed complement would hybridize to SEQ ID NO:1 or 2.

In addition, claim 74 encompasses an unrelated sequence that share a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, said sequence hybridizes to unrelated sequences attached to the polynucleotide sequence encoding the polypeptide fragment consisting of SEQ ID NO:3.

Further, a PBR gene encoding a PBR protein that "comprises" the mutant residues threonine 147 or arginine 162, or that "comprises" SEQ ID NO:3 encompasses variant PBR gene with unknown structure encoding variant PBR protein that contains the mutant residues threonine 147 or arginine 162, or that contains the polypeptide fragment of SEQ ID NO:3.

Similarly, "a PBR gene" of claim 74 encompasses any variant PBR gene with unknown structure.

One does not know how to make the claimed complement, or sequence that share a fragment of 7 to 40 nucleotides of SEQ ID NO:1 or 2, in view that their structure is unknown.

Further, one cannot predict the structure of the full length PBR polynucleotide variant "comprising" SEQ ID NO:1 or 2, nor the structure of variant PBR polynucleotide encoding a PBR protein that "comprises" the mutant residues threonine 147 or arginine 162, or that "comprises" SEQ ID NO:3, nor the structure of any variant PBR gene, in view of the teaching of Harris et al, and Cawthon et al, of record, that that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined.

II) Applicant further argues that it is well within the skill in the art to screen for sequences that inhibit expression of a particular gene, and that the fact that the outcome of a screening program to identify 7 to 40 nucleotides of the complement of SEQ ID NO:1 or 2 that inhibit expression of a PBR nucleic acid may be unpredictable, is precisely why a program is carried out.

Applicant argues that screening to locate biomolecules with particular properties, such as antibody, as in *In re Wands*, or *Hybritech Inc. v. Monoclonal antibodies Inc.,* does not constitute undue experimentation.

Applicant's arguments set forth in paper of 06/29/05 have been considered but are not deemed to be persuasive for the following reasons:

One cannot predict that there exists within the cDNA fragment consisting of SEQ ID NO:1 or 2 active small antisense sequence(s), such as that of 7 to 40 nucleotides, that could inhibit expression of PBR gene encoding SEQ ID NO:3, in view that the position of the active, inhibitory antisense sequence on a gene could not be predicted, as taught by US 5,585,479, of record, and in view that SEQ ID NO:1 or 2 encoding SEQ ID NO:3 are only cDNA fragments and that the structure of the mutated, full length mutated PBR gene comprising the mutated fragment consisting of SEQ ID NO:1 or 2 is not known.

Therefore, one cannot predict nor have a reasonable expectation of success of obtaining active, inhibitory small antisense sequence(s), such as that of 7 to 40 nucleotides, within the cDNA fragment consisting of SEQ ID NO:1 or 2, that could inhibit cell proliferation.

Further, it is noted that in a recent court case, *Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004, the court teaches that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 112, first paragraph rejection, claims 74-75, 77-80 are still rejected under 112, first paragraph, for **lack of enablement for a "pharmaceutical composition" comprising a nucleic acid that is complementary to SEQ ID NO:1 or 2 or is a fragment of 7 to 40 nucleotides thereof, for reasons already of record in paper of 12/27/04.**

It is noted that "a pharmaceutical composition" reads on in vivo use thereof.

It is unpredictable that the claimed nucleic acids could be successfully used *in vivo*, such as in vivo inhibition of cell proliferation, as contemplated, because although the art teaches that some antisenses could inhibit expression of target genes in vivo, the behavior and effect of antisense oligonucleotide in vivo is not predictable, and even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss (of record). Similarly, Branch, AD, 1998 (of record) teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p50, first column).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102, NEW REJECTION

Claim 81 is rejected under 35 UCS 102(e) as being anticipated by US 5,663,062 or US 5,407,799.

Claim 81 is drawn to an isolated nucleic acid consisting of the complement of SEQ ID NO:1 or 2.

US 5,663,062 teaches a library of oligonucleotides, containing every possible combination of nucleotide sequence, wherein the library members (the oligonucleotides in the library) have the same length, and are from 6 to 10 nucleotides in length, e.g. a 9 mer library (US 5,663,062, abstract, column 2, Summary, column 4, lines 26-27, 34).

US 5,407,799 teaches primers libraries, such as octamer, nonamer or decamer libraries (column 16, under Primer libraries).

In view of the teaching of US 5,663,062 or US 5,407,799, one would readily envision the claimed complement.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

SUSAN UNGAR, PH.D
PRIMARY EXAMINER